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Biannual Fluoride Varnish Applications and Caries Incidence in Preschoolers: A 24-month Follow-Up Randomized Placebo-Controlled Clinical Trial

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Key Words
Controlled clinical trial · Dental caries · Preschool children · Primary dentition · Topical fluoride

Abstract
Sound evidence on the effectiveness of fluoride varnishes (FV) to reduce caries incidence in preschool children is lacking. ***Objective:*** To assess whether the application of FV in preschool children at 6-month intervals decreases the incidence of caries and produces any adverse effects. ***Methods:*** A randomized, examiner- and patient-blind, placebo-controlled, parallel-group design, clinical trial, comprising 1- to 4-year-old children, 100 in each group (FV or placebo varnish, PV), was conducted in Rio de Janeiro, Brazil. Two trained pediatric dentists performed the clinical examinations (kappa = 0.85). Dental caries was recorded at the d_2 (cavitated enamel) and d_3 (dentine) levels using the International Caries Diagnosis and Assessment System. ***Results:*** At baseline, the mean age of the participants was 2.4 years (SD 0.9) and the mean $d_3$mfs was 0.8 (SD 1.9). Most of the children brushed their teeth with fluoride toothpaste and consumed fluoridated tap water. After 24 months, 89 and 92 children of the test and the control groups were analyzed, respectively. A total of 32 (35.9%) children in the FV group and 43 (46.7%) in the PV group presented new dentine caries lesions (χ^2 test; p = 0.14), showing relative and absolute risk reductions of 23% (95% CI: –9.5 to 45.9) and 11% (95% CI: –3.5 to 25.0). The mean caries increment differences between the test and control groups were –0.8 (95% CI: –2.0 to 0.4) at the d_2 level and –0.7 (95% CI: –1.9 to 0.4) at the d_3 level. Only 2 minor complaints regarding the intervention were reported. ***Conclusion:*** Although safe and well accepted, twice-yearly professional FV application, during 2 years, did not result in a significant decrease in caries incidence.

Dental caries in primary dentition is an important public health problem in many countries and minority and low-income children have greater likelihood of having untreated caries, thus experiencing negative effects on their oral health-related quality of life [Vargas et al., 1998; Declerck et al., 2008; Leake et al., 2008; Dye and Thornton-Evans, 2010; Goettems et al., 2011; Brasil Ministério da Saúde, 2011].

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Fluoride varnishes (FV) were introduced into dental practice in the 1970s. Both the European Academy of Paediatric Dentistry [2009] and the American Academy of Pediatric Dentistry [2012a] endorse the use of FV 2–4 times a year for caries prevention in primary and permanent teeth. Moreover, FV use has been expanding in non-dental settings as part of individual and community-based caries preventive protocols [Weintraub, 2003; Divaris et al., 2013]. However, there is currently mixed evidence as to the additional benefit of periodic professional topical fluoride applications in populations with access to fluoridated water and toothpaste [American Dental Association, 2006].

Systematic reviews provide the foundation for evidence-based clinical practice [Ijaz et al., 2010] and a few have addressed the effects of FV on caries prevention in children [Bader et al., 2001, 2004; Rozier, 2001; Strohmenger and Brambilla, 2001; Marinho et al., 2002; Petersson et al., 2004; Azarpazhooh and Main, 2008; Carvalho et al., 2010]. The efficacy of FV for caries prevention in permanent dentition is undisputable but the strength of the evidence for its efficacy in the primary dentition of preschool children can be rated as fair, at best. Notably, Marinho et al. [2002], in their Cochrane review, estimated the pooled preventive fraction of FV in the primary teeth to be 33% (95% CI: 19–48) but they stressed the need for caution in interpreting their data due to the preponderance of no treatment control and low methodological quality of the studies in their review. Surprisingly, most of the recommendations regarding the use of FV in preschool children are based on the results of one pivotal trial [Weintraub et al., 2006] which enrolled only caries-free children, did not use a true placebo and had a high attrition rate. Increasing emphasis on the need for evidence-based health interventions requires the evaluation of the efficacy of FV in preschoolers by a carefully designed randomized controlled trial that uses a true placebo and may generate sound data in this area.

The objective of this 2-year randomized placebo-controlled trial was to assess whether the application of FV in preschool children at 6-month intervals decreases the incidence of caries lesions in the primary dentition and whether it is safe and well accepted.

Methods

Ethical approval was obtained from the Research Ethics Committee of Pedro Ernesto Hospital/Rio de Janeiro State University and the trial protocol was registered at the National Council on Ethics in Human Research, Ministry of Health, Brazil (CAAE 0048.0.228.000-07). The children's parents/caregivers read and signed an informed consent form prior to participation in the study. Parents/caregivers were assured that their children could withdraw from the study at any time without negative consequences.

Trial Design

This study was a prospective, randomized, examiner- and patient-blind, placebo-controlled, parallel-group clinical trial.

Participants

Participants were children from low-income families recruited at a pediatric ambulatory clinic located in a public health center in Rio de Janeiro, Brazil. They had access to fluoridated drinking water through the public water supply system and to free basic dental care under the Brazilian public health system. Affordable fluoride toothpastes are available in Brazil [Goldman et al., 2008].

Inclusion criteria for enrollment were as follows: age 1–4 years, living in Rio de Janeiro for at least 1 year and planning to reside in the city for the following 2 years, having a fixed address, and owning a telephone or having a close relative who owned a telephone. Children were excluded if they had received a professional fluoride application in the previous 6 months, presented more than 10 dental surfaces with dentine caries lesions, had a dental abscess or had a systemic disease that could be aggravated by a dental problem.

Intervention

Interviews

At the beginning of the trial, caregivers of the children enrolled attended an oral health educational session. The sessions were held in a conference room at the public health center that could accommodate up to 30 people. Caregivers received information regarding dental caries etiology and prevention and were encouraged to brush their children's teeth with small amounts of fluoride toothpaste daily and to reduce the consumption of sugary snacks. Then, at each follow-up visit, individual oral health counseling, including supervised toothbrushing, was provided. Children also received a toothbrush and fluoride toothpaste containing 1,450 ppm sodium monofluorophosphate (Colgate Máxima Proteção Anticáries; Colgate-Palmolive, São Bernardo do Campo, Brazil) at baseline examination and at each follow-up visit.

At baseline, the caregivers were interviewed in order to collect information about the children's sociodemographic characteristics, toothbrushing behavior, use of fluoride toothpaste, toothache in the previous 6 months and lifetime dental experience. Socioeconomic status was measured using the Brazil Economic Classification Criteria [Associação Brasileira de Empresas de Pesquisa, 2008], which categorizes people into 5 socioeconomic categories (A and B: high socioeconomic status, C: medium socioeconomic status, D and E: low socioeconomic status).

At each follow-up visit, parents were asked whether their children had had dental pain or a dental abscess related to caries since their last follow-up examination.

At 1 week after the first varnish application, parents/caretakers were interviewed by telephone regarding possible side effects and the acceptability of the procedure. They were asked whether, on the day of the varnish application, the child complained of a burning sensation in their mouth, or experienced nausea, altered taste or allergies such as asthma, rhinitis and skin rash. Information was also sought about whether anyone in the family felt bothered by

the yellowish color of the child's teeth after the varnish application and whether the child avoided smiling because of the discoloration of his/her teeth.

Examinations

Prior to each dental examination, the children had their teeth brushed by their caregivers under professional supervision. All children were examined at the dental office, with optimal lighting and after having their teeth dried with compressed air. Two trained pediatric dentists performed the clinical examinations at baseline and every 6 months. They were unaware of the treatment group to which subjects were assigned. Dental caries was assessed according to the Caries Diagnosis and Assessment System criteria (ICDAS II) using World Health Organization probes and plane surface dental mouth mirrors. Clinical diagnosis by visual inspection and tactile examination was not confirmed by X-rays. Interexaminer reliability was assessed by reexamining 12 and 27 subjects at baseline and at the 12-month follow-up, respectively. Children presenting dental caries at baseline and at any follow-up examination were referred for dental care. Dental treatments provided included glass ionomer and resin restorations, pulpotomies, root canal treatment and extractions.

Varnish Application

Children enrolled in the trial received 5% sodium FV (Duraphat, Colgate Oral Pharmaceuticals, New York, N.Y., USA) or a placebo varnish (PV; Colgate Oral Pharmaceuticals) application at baseline and every 6 months for a period of 24 months. The FV was purchased from a dental supplier and the PV was provided by the FV manufacturer. The placebo was identical to the active varnish except that it did not contain fluoride and it was packaged in a tube identical to the tube containing the active varnish. The varnish applications were performed by undergraduate or graduate dental students who had been previously trained. The students were not involved in the examinations of the children and they did not know whether they were applying FV or PV.

Before varnish application, each child's teeth were brushed by the dental student without using toothpaste. A drop of varnish, the size of a small pea, for children with full temporary dentition, and approximately half this amount for children with 10 teeth or less, was dispensed onto a paper pad. After cotton roll isolation, the child's teeth were dried with compressed air and the varnish was applied to all tooth surfaces with a disposable microbrush. The parents/caregivers were instructed to avoid giving their children hard food and not to brush their teeth on the day of the treatment.

Outcomes

Dental caries was recorded at d_2 (cavitated caries lesion in enamel or in dentine) and d_3 (dentine caries lesions only) detection thresholds and caries severity was expressed as the number of tooth surfaces in the primary dentition that were decayed, filled and extracted due to caries ($d_2$mfs or $d_3$mfs). In order to compute $d_2$mfs, tooth surfaces that received ICDAS codes 3, 5 or 6 were considered carious and for $d_3$mfs computation only surfaces with ICDAS codes 5 or 6 were considered carious. When a tooth was verified as extracted as a result of caries, 4 and 5 surfaces were recorded as missing owing to caries for anterior and posterior teeth, respectively.

The primary outcome was caries incidence as measured by the proportion of children developing any new dentine caries during the study. The number of dental surfaces that were decayed, filled and extracted due to caries (d_3mfs_{ini}) at baseline was subtracted from the number of dental surfaces that were decayed, filled and extracted due to caries at the 24-month follow-up (d_3mfs_{fin}). A child was considered to be an incident case of dental caries if he/she had $d_3mfs_{fin} - d_3mfs_{ini} > 0$.

A secondary outcome was the 24-month caries increment, as measured by the change from baseline in the dmfs index at d_2 and d_3 caries detection thresholds.

Sample Size

Based on data for caries incidence in preschool children attending the dental clinic located in the public health center where the study was conducted, sample size was planned to detect caries incidence of 33 and 15% in the control and test groups, respectively, with alpha = 0.05 and power = 0.80. Thus, 85 subjects would have to be enrolled in each group [Pocock, 1988]. Considering an attrition rate of 15%, sample size was increased to 200 subjects (100 in each group).

Randomization

A randomization list, based on a sequence of random numbers generated by MS Excel software (Microsoft Corp, Redmond, Wash., USA) was used by a professional not involved in the varnish application or the clinical examination to assign each child to test and control groups. Block randomization was performed (n = 10).

Blinding

The placebo and the active varnish tubes were covered with an opaque white plastic tape and were coded A or Z by a person who was not involved in the trial. The randomization codes were kept in a sealed envelope until the end of the follow-up period. The participants, their caregivers, examining dentists and all the clinical staff remained blinded to treatment allocation throughout the trial.

Statistical Methods

Data were analyzed using Stata software, version 9.0 (StataCorp, College Station, Tex., USA). The level of statistical significance was set at 0.05. Interexaminer reproducibility at the tooth surface level was measured by Cohen's kappa coefficient. Descriptive analysis was performed to summarize the clinical and sociodemographic characteristics of each group at baseline in order to assess how comparable the groups were at the beginning of the study. The χ^2 test was used to assess the difference in the proportion of children with new dentine caries lesions in the test and control groups. Differences in mean $d_2$mfs and $d_3$mfs between the test and control groups were evaluated using the t test. Post hoc secondary analyses were conducted to assess the effectiveness of FV application according to baseline caries status and number of varnish applications.

Results

Enrollment took place from July 2006 to July 2007. In total, 310 children were invited to participate; 230 showed up for an interview and oral examination; 29 did not meet the inclusion criteria and 1 was excluded because of uncooperative behavior during the dental appointment.

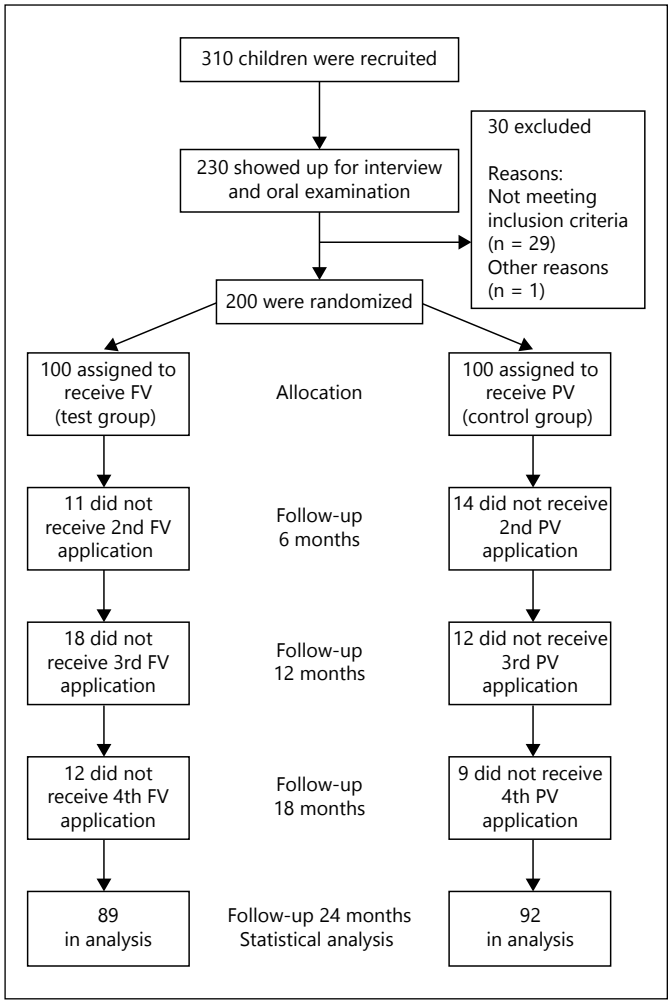

Fig. 1. Trial flowchart.

Those cases where inclusion criteria were not met were as follows: 1 child was outside the age range, 1 child intended to move to another town in the following year, 1 child had a systemic disease, 7 children had no fixed address, 9 children had more than 10 dentine caries lesions and 10 children had received a professional fluoride application in the previous 6 months. A protocol violation occurred: 1 child who had had a topical fluoride application during the 6 months before the trial was included. This child was allocated to the FV group but she dropped out of the study after 12 months. She was thus not included in the final statistical analysis.

The flow of participants in each phase of the study is shown in figure 1. Follow-up ended in September 2009. At the end of the study, a total of 181 (90.5% of all subjects randomized) children had shown up for the 24-month follow-up examination. The main reason for loss to follow-up was inability of the research team to contact the family of the child.

All 200 participants who underwent randomization received the intervention at baseline as allocated. However, not all 181 children who were analyzed received the 4 programmed varnish applications. In the FV group (n = 89), 75 (84.3%) children received 4 applications, 9 (11.1%) children received 3 applications, 3 (3.4%) children received 2 applications and 2 (2.2%) children received 1 application. In the PV group (n = 92), 78 (84.8%) children received 4 applications, 11 (11.9%) children received 3 applications and 3 (3.3%) children received 2 applications.

Baseline Characteristics of the Participants

Almost all participants (193; 96.5%) were exposed to fluoridated drinking water and 159 (79.5%) reported brushing their teeth with fluoride toothpaste. A total of 26 children had already visited a dentist (24 for dental examinations and preventive services and 2 for dental extractions), 47 children (23.5%) had at least 1 dental surface with a caries lesion in dentine and no children presented restored or sealed teeth. The caregivers of 12 children (6%) reported that the child had had toothache in the 6 months before the beginning of the study. At baseline, the test and control groups presented similar demographic and clinical characteristics (table 1).

The clinical interexaminer reproducibility for dental caries was very good [Altman, 1991] both at baseline (Cohen's kappa coefficient = 0.85) and at the 12-month follow-up (Cohen's kappa coefficient = 0.87). Reliability assessment at the 24-month follow-up was not done.

The primary analysis was intention-to-treat and included all patients who showed up for the 24-month follow-up oral examination, regardless of whether or not they had received all 4 scheduled varnish applications. The demographic and clinical characteristics at baseline of the analyzed and lost to follow-up participants are shown in table 2.

Caries Incidence

Overall, 75 of the 181 children examined at the end of the study (41.4%) had developed new dentine carious lesions. The number of children with new caries lesions in dentine was greater in the control than in the test group but this difference was not statistically significant (table 3). Although not significant, the FV yielded a relative risk reduction for dentine dental caries of 23% (95% CI: –9.5 to 45.9) and an absolute risk reduction of 11% (95% CI: –3.5 to 25.0) compared with the PV; this means

Table 1. Characteristics of the participants randomized to the FV and PV groups at baseline

Characteristic	FV group (n = 100)	PV group (n = 100)	All children (n = 200)
Gender, n			
Female	50 (50)	43 (43)	93 (47)
Male	50 (50)	57 (57)	107 (53)
Socioeconomic status, n			
B	9 (9)	4 (4)	13 (6.5)
C	57 (57)	65 (65)	122 (61.0)
D or E	33 (33)	29 (29)	62 (31.0)
Not provided	1 (1)	2 (2)	3 (1.5)
Age, years			
Mean ± SD	2.5±0.8	2.3±0.9	2.4±0.9
Range	1.0–3.9	1.0–4.0	1.0–4.0
Use of fluoride toothpaste, n			
Yes	84 (84)	75 (75)	159 (79.5)
No	15 (15)	23 (23)	38 (19)
Not informed	1 (1)	2 (2)	3 (1.5)
Dental caries status			
$d_2$mfs (mean ± SD)	0.7±1.7	1.2±2.4	0.9±2.1
$d_3$mfs (mean ± SD)	0.6±1.6	1.0±2.1	0.8±1.9
Children with dentine caries, n	21 (21)	26 (26)	47 (24)

Values in parentheses indicate percentages. $d_2$mfs: number of cavitated decayed (enamel + dentine), filled and extracted dental surfaces in primary teeth. $d_3$mfs: number of cavitated decayed (dentine), filled and extracted dental surfaces in primary teeth.

Table 2. Characteristics at baseline of the children in the FV and PV groups who remained in the study and were examined at the 24-month follow-up and characteristics at baseline of all participants who were lost to follow-up

Characteristic	FV group (n = 89)	PV group (n = 92)	Children lost to follow-up (n = 19)
Gender, n			
Female	44 (49.4)	41 (44.6)	8 (42.1)
Male	45 (50.6)	51 (55.4)	11 (57.9)
Socioeconomic status, n			
B	8 (9.0)	4 (4.4)	2 (10.5)
C	50 (56.2)	59 (64.1)	12 (63.2)
D or E	30 (33.7)	28 (30.4)	5 (26.3)
Not provided	1 (1.1)	1 (1.1)	0
Age, years			
Mean ± SD	2.5±0.8	2.3±0.9	2.3±0.8
Use of fluoride toothpaste, n			
Yes	76 (85.4)	68 (73.9)	15 (78.9)
No	12 (13.5)	22 (23.9)	4 (21.1)
Not informed	1 (1.1)	2 (2.2)	0
Dental caries status			
$d_3$mfs (mean ± SD)	0.6±1.5	1.0±2.0	1.0±2.1
Children with dentine caries, n	17 (19.1)	24 (26.1)	6 (31.6)

Values in parentheses indicate percentages. $d_3$mfs: number of cavitated decayed (dentine), filled and extracted dental surfaces in primary teeth.

Table 3. Comparison of caries incidence and caries increment in the FV and PV groups at the 24-month follow-up

Outcome	FV group (n = 89)	PV group (n = 92)	Difference (95% CI)	p value
Primary endpoint				
Children with new dentine caries lesions, n	32 (35.9%)	43 (46.7%)	−10.8 (−24.9 to 3.3)	0.14[1]
Secondary endpoints				
$d_2$mfs (mean ± SD)	2.0±4.0	2.8±4.2	−0.8 (−2.0 to 0.4)	0.19[2]
$d_3$mfs (mean ± SD)	1.8±3.9	2.5±4.0	−0.7 (−1.9 to 0.4)	0.23[2]

$d_2$mfs: number of cavitated decayed (enamel + dentine), filled and extracted dental surfaces in primary teeth. $d_3$mfs: number of cavitated decayed (dentine), filled and extracted dental surfaces in primary teeth.
[1] χ^2 test. [2] t test.

that, had it been significant, it would be necessary to treat 9 children to avoid caries in 1 child.

Of those who did not show up for the 24-month examination, 4 subjects were checked at the 6-month and 18-month follow-ups and presented dentine caries lesions. Thus, including these patients' data, caries incidence estimates increased to 37.4% (34/91) and 47.9% (45/94) in the test and control groups, respectively, but the difference between the groups was still not significant (χ^2 test; p = 0.15).

A post hoc analysis stratifying the sample by caries experience at baseline ($d_3$mfs >0 or $d_3$mfs = 0 at baseline) showed that caries incidence was higher in children who had caries experience at baseline (82.3 and 83.3% in FV and PV groups, respectively; χ^2 test; p = 0.93) than in children who did not have caries experience at baseline (25.0 and 33.8% in FV and PV groups, respectively; χ^2 test; p = 0.25). Nevertheless, the differences in caries incidence between FV and PV groups in children who had or did not have caries experience at baseline were not statistically significant.

Similarly, a comparison of caries incidence in those children who received the maximum number of varnish applications and those who did not demonstrated no statistically significant differences between FV and PV groups (all 4 programmed varnish applications, caries incidence: FV = 36.0%; PV = 44.9%; χ^2 test; p = 0.26; less than four varnish applications, caries incidence: FV = 35.7%; PV = 57.1%; χ^2 test; p = 0.26).

Caries Increment

The number of dental surfaces with new dentine caries lesions as measured by the $d_3$mfs increment was greater in the control than in the test group but the difference was not statistically significant. When cavitated enamel lesions were included in the analysis ($d_2$mfs), the difference in caries increment between the two groups remained statistically not significant (table 3). The caries preventive fractions for children receiving FV were 28.6% (95% CI: 22.3–34.7) and 28.0% (95% CI: 24.7–34.4) at d_2 and d_3 caries detection thresholds, respectively.

Dental Pain and Abscess

Within the 24 months, no significant differences were found between the test and control groups in the frequencies of dental pain (FV: n = 11, 12.4%; PV: n = 11, 12.0%; p = 0.93) and dental abscess due to caries (FV: n = 2, 2.2%; PV: n = 1, 1.1%; p = 0.54).

Adverse Events

Only 2 complaints were reported. The father of 1 child who belonged to the test group reported that when the child returned home after this first FV application, the mother felt bothered by the color of child's teeth; the mother of 1 child who belonged to the control group reported that her child complained of a burning sensation in her mouth on the day of this first PV application. There were no withdrawals from the study due to adverse effects of the FV or PV. In addition, 8 children in the test group and 3 children in the control group reported having asthma at baseline but none of them reported an adverse effect.

Discussion

This study was unable to demonstrate that twice-yearly professional application of FV during 2 years in low-income, 1- to 4-year-old Brazilian children who reported

using fluoride toothpaste and lived in a city where fluoridated drinking water was available, significantly decreased caries incidence in the primary dentition. On the other hand, our results provided evidence that the intervention is safe and well accepted by the children themselves and their caregivers.

At the end of the study, caries prevalence (55.8%) was higher than the estimate for 5-year-old children living in Southeastern Brazil (48.1%) reported in the National Oral Health Survey conducted in 2010 [Brasil Ministério da Saúde, 2011]. Smaller-scale studies that estimated caries prevalence in preschoolers living in fluoridated communities in Southern and Southeastern Brazil have found figures ranging from 40% [Ferreira et al., 2007] to 45.3% [Borges et al., 2012], depending on the age of the subjects. This means that, although children with a dental abscess or more than 10 carious dental surfaces were not included, the study participants were still a group of preschoolers at high risk of developing dental caries.

The latest published FV randomized controlled trial that used an individual strategy of randomization was completed in 2004. It included only caries-free, 6- to 44-month-old children living in a fluoridated community [Weintraub et al., 2006]. That study found a statistically significant difference in caries incidence between children who received and those who did not receive FV applications twice a year. However, considering the total number of children submitted to any follow-up examination during the course of the study (n = 193), only 36.5% of the participants experienced caries during the 24-month follow-up period. More recently, a secondary analysis of data from a community-randomized controlled trial [Divaris et al., 2013] among 3- to 5-year-old Aboriginal children in Australia, exposed to varying concentrations of fluoride in drinking water, showed substantial heterogeneity in FV efficacy by baseline surface caries status and small differences in benefit by type of tooth surface. In our study, a post hoc analysis by caries experience at baseline ($d_3mfs > 0$ or $d_3mfs = 0$) showed a greater difference in caries incidence between the test and control groups in children who were caries free (8.8%) than in children who had dental caries (1%) at baseline. Altogether, these findings suggest that the anticaries effect of FV may be greater in children with more sound dental surfaces than in children with active disease or hypoplastic enamel. Therefore, current recommendations [American Dental Association, 2006; American Academy of Pediatric Dentistry, 2012a] on targeting FV applications to children at moderate or high risk of caries may need to be revised. Future studies should be designed not only to investigate the degree of the protective effect that could be obtained from professional FV applications but also to assess who could benefit the most from this type of intervention.

An important limitation of the present study is the wide confidence interval of its primary endpoint. Caries incidence was higher than expected in both the test and control groups but the difference between the groups was approximately 60% of the difference that was initially expected. Considering the observed caries incidences, in order to have 80% power to detect a statistically significant difference in the frequencies of individuals developing new dentine caries in the test and control groups, if such a difference existed, at least 332 children should have been enrolled in each group. Consequently, the absence of a statistically significant difference between the two groups must not be seen as evidence that the tested treatment had no effect.

To specify what would be the smallest difference of clinical relevance in caries incidence among children submitted or not to a given preventive intervention (e.g. twice-yearly FV applications) is not an easy task [Alderson, 2004] and we may have overestimated the expected benefit of FV based on the overly optimistic preventive fractions estimates that have been reported by the FV clinical trials conducted in recent years [Carvalho et al., 2010]. Worthy of note were the statistically nonsignificant differences in caries incidence among test and control Aboriginal preschool children in two different 2-year cluster-randomized controlled trials – one in Canada [Lawrence et al., 2008] and another in Australia [Slade et al., 2011].

It is possible that, nowadays, twice-yearly professional FV applications to the primary dentition of preschool children confer only limited anticaries benefit on top of that already provided by fluoride toothpastes, especially in children with low caries prevalence. Moreover, it is not clear whether this benefit is clinically meaningful [Marinho et al., 2004]. In the present study, similar increases in the number of dental surfaces with cavitated lesions at both enamel and dentine levels were observed in children exposed and not exposed to professional fluoride therapy in addition to fluoride toothpaste use at home.

To the best of our knowledge, this is the first randomized controlled clinical trial testing the effectiveness of an FV that used a placebo similar to the active varnish in all aspects but without fluoride. Placebos should always be inert treatments intended to have no effect other than the psychological benefit of offering treatment, which itself can be a powerful effect [Rothman and Greenland, 1998]. It has long been recognized that the placebo provides an

indispensable tool for determining the true effect of a health intervention and can have an effectiveness of up to 35% [Beecher, 1955]. The underlying mechanism of the placebo effect has yet to be well established. The response to a placebo could be a basic physiological process such as release of neurotransmitters or alterations in immune system activity or could also be some more complex process including change in mood or motivation/effort. For example, health-related self-efficacy may be one mechanism of the placebo effect [Oken, 2008]. Self-efficacy has been shown to be a strong predictor of sugar intake in low-income preschool children, that is, mothers who are more confident in their ability to care for their teeth have children with lower sugar intake [Litt et al., 1995]. This could be one of the many plausible explanations for a decrease in caries incidence in children participating in a caries FV preventive trial; hence the relevance of the placebo.

Previous systematic reviews [Marinho et al., 2002; Carvalho et al., 2010] have highlighted the need to investigate more thoroughly the acceptability of the FV treatment and its possible side effects. In one study that tested a product containing 0.1% fluoride, 0.9% w/w difluorosilane (Fluor Protector; Vivacare/Vivadent, Schaan, Liechtenstein), a few children complained of a somewhat bitter taste and no side effects were noted [Twetman et al., 1996]. In a study using Duraphat (Colgate Oral Pharmaceuticals) [Weintraub et al., 2006] only 1 adverse event was reported: an ulcer on a child's cheek that developed 2 months after the last FV application, which was 'fluoride-free'. In the same study, none of the FV recipients who were asthmatic had adverse events. In the present study, only 2 complaints were reported: 1 about the yellowish color of the FV and another of a 'burning sensation' in the mouth in a child who received the PV. This sensation was probably caused by ethanol, a substance that is used as a solvent in the varnish [Strohmenger and Brambilla, 2001]. Although it was not a prespecified outcome, children's behavior during varnish applications was evaluated by consulting the patient's dental records. Using Frankl's Behavioral Rating Scale [American Academy of Pediatric Dentistry, 2012b], dental students who served as operators throughout the trial recorded children's behavior during their dental appointments as: 'definitely negative', 'negative', 'positive' or 'definitely positive'. We noticed that the frequency of 'definitely negative' and 'negative' ratings dropped from 46.5% on the 1st varnish application to 6.0% on the 5th varnish application performed at the 24-month dental examination. Thus, our findings support the safety and acceptability of the intervention but also show that 1- to 4-year-old children may be initially reluctant or even refuse to cooperate during FV applications.

Attempts to maintain a high level of participation included cards and telegrams sent home and frequent contacts made by telephone. Loss to follow-up was low (slightly higher in the test group than in the control group) and attrition in both groups was due to reasons unrelated to the intervention. At baseline, the children analyzed at the 24-month follow-up were similar to the children initially randomized to the test and control groups in terms of sociodemographic characteristics, frequency of use of fluoride toothpaste and caries status. In addition, the proportion of test and control children who received the full set of varnish applications was over 80% and almost the same in the two groups.

This study provided some new relevant information in relation to the safety and acceptability of FV application but, despite having been carefully designed in accordance with the CONSORT recommendations [Moher et al., 2010], it could not produce conclusive evidence for an anticaries effect of FV therapy in preschool children.

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Disclosure Statement

The authors declare no potential conflict of interest.

References

Alderson P: Absence of evidence is not evidence of absence. BMJ 2004;328:476–477.

Altman DG: Practical Statistics for Medical Research, ed 1. London, Chapman & Hall, 1991.

American Academy of Pediatric Dentistry: Guideline on fluoride therapy. Pediatr Dent 2012a;34:12–13.

American Academy of Pediatric Dentistry: Guideline on behavior guidance for the pediatric dental patient. Pediatr Dent 2012b;34:170–182.

American Dental Association: Professionally applied topical fluoride: evidence-based clinical recommendations. J Am Dent Assoc 2006;137:1151–1159.

Associação Brasileira de Empresas de Pesquisa: Critério de classificação econômica Brasil, 2008. www.abep.org/novo/FileGenerate.ashx?id=250.

Azarpazhooh A, Main PA: Fluoride varnish in the prevention of dental caries in children and adolescents: a systematic review. J Can Dent Assoc 2008;74:73–79.

Bader JD, Rozier RG, Lohr KN, Frame PS: Physicians' roles in preventing dental caries in preschool children: a summary of the evidence for the US Preventive Services Task Force. Am J Prev Med 2004;26:315–325.

Bader JD, Shugars DA, Bonito AJ: A systematic review of selected caries prevention and management methods. Community Dent Oral Epidemiol 2001;29:399–411.

Beecher HK: The powerful placebo. J Am Med Assoc 1955;159:1602–1606.

Borges HC, Garbin CA, Saliba O, Saliba NA, Moimaz SA: Socio-behavioral factors influence prevalence and severity of dental caries in children with primary dentition. Braz Oral Res 2012;26:564–570.

Brasil Ministério da Saúde: SB Brasil 2010. Pesquisa nacional de saúde bucal – principais resultados. Brasília, Ministério da Saúde, 2011.

Carvalho DM, Salazar M, Oliveira BH, Coutinho ES: Fluoride varnishes and decrease in caries incidence in preschool children: a systematic review. Rev Bras Epidemiol 2010;13:139–149.

Declerck D, Leroy R, Martens L, Lesaffre E, Garcia-Zattera MJ, Vanden Broucke S, Debyser M, Hoppenbrouwers K: Factors associated with prevalence and severity of caries experience in preschool children. Community Dent Oral Epidemiol 2008;36:168–178.

Divaris K, Preisser JS, Slade GD: Surface-specific efficacy of fluoride varnish in caries prevention in the primary dentition: results of a community randomized clinical trial. Caries Res 2013;47:78–87.

Dye BA, Thornton-Evans G: Trends in oral health by poverty status as measured by healthy people 2010 objectives. Public Health Rep 2010;125:817–830.

European Academy of Paediatric Dentistry: Guidelines on the use of fluoride in children: an EAPD policy document. Eur Arch Paediatr Dent 2009;10:129–135.

Ferreira SH, Beria JU, Kramer PF, Feldens EG, Feldens CA: Dental caries in 0- to 5-year-old Brazilian children: prevalence, severity, and associated factors. Int J Paediatr Dent 2007;17:289–296.

Goettems ML, Ardenghi TM, Romano AR, Demarco FF, Torriani DD: Influence of maternal dental anxiety on oral health-related quality of life of preschool children. Qual Life Res 2011;20:951–959.

Goldman AS, Yee R, Holmgren CJ, Benzian H: Global affordability of fluoride toothpaste. Global Health 2008;4:7.

Ijaz S, Croucher RE, Marinho VC: Systematic reviews of topical fluorides for dental caries: a review of reporting practice. Caries Res 2010;44:579–592.

Lawrence HP, Binguis D, Douglas J, McKeown L, Switzer B, Figueiredo R, Laporte A: A 2-year community-randomized controlled trial of fluoride varnish to prevent early childhood caries in Aboriginal children. Community Dent Oral Epidemiol 2008;36:503–516.

Leake J, Jozzy S, Uswak G: Severe dental caries, impacts and determinants among children 2–6 years of age in Inuvik Region, Northwest Territories, Canada. J Can Dent Assoc 2008;74:519.

Litt MD, Reisine S, Tinanoff N: Multidimensional causal model of dental caries development in low-income preschool children. Public Health Rep 1995;110:607–617.

Marinho VC, Higgins JP, Logan S, Sheiham A: Fluoride varnishes for preventing dental caries in children and adolescents. Cochrane Database Syst Rev 2002;3:CD002279.

Marinho VC, Higgins JP, Sheiham A, Logan S: Combinations of topical fluoride (toothpastes, mouthrinses, gels, varnishes) versus single topical fluoride for preventing dental caries in children and adolescents. Cochrane Database Syst Rev 2004;1:CD002781.

Moher D, Hopewell S, Schulz KF, Montori V, Gotzsche PC, Devereaux PJ, Elbourne D, Egger M, Altman DG: Consort 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. J Clin Epidemiol 2010;63:e1–e37.

Oken BS: Placebo effects: clinical aspects and neurobiology. Brain 2008;131:2812–2823.

Petersson LG, Twetman S, Dahlgren H, Norlund A, Holm AK, Nordenram G, Lagerlof F, Soder B, Kallestal C, Mejare I, Axelsson S, Lingstrom P: Professional fluoride varnish treatment for caries control: a systematic review of clinical trials. Acta Odontol Scand 2004;62:170–176.

Pocock JS: Clinical Trials – a Practical Approach. New York, Wiley, 1988.

Rothman KJ, Greenland S: Modern Epidemiology. Philadelphia, Lippincott-Raven, 1998.

Rozier RG: Effectiveness of methods used by dental professionals for the primary prevention of dental caries. J Dent Educ 2001;65:1063–1072.

Slade GD, Bailie RS, Roberts-Thomson K, Leach AJ, Raye I, Endean C, Simmons B, Morris P: Effect of health promotion and fluoride varnish on dental caries among Australian Aboriginal children: results from a community-randomized controlled trial. Community Dent Oral Epidemiol 2011;39:29–43.

Strohmenger L, Brambilla E: The use of fluoride varnishes in the prevention of dental caries: a short review. Oral Dis 2001;7:71–80.

Twetman S, Petersson LG, Pakhomov GN: Caries incidence in relation to salivary mutans streptococci and fluoride varnish applications in preschool children from low- and optimal-fluoride areas. Caries Res 1996;30:347–353.

Vargas CM, Crall JJ, Schneider DA: Sociodemographic distribution of pediatric dental caries: NHANES III, 1988–1994. J Am Dent Assoc 1998;129:1229–1238.

Weintraub JA: Fluoride varnish for caries prevention: comparisons with other preventive agents and recommendations for a community-based protocol. Spec Care Dentist 2003;23:180–186.

Weintraub JA, Ramos-Gomez F, Jue B, Shain S, Hoover CI, Featherstone JD, Gansky SA: Fluoride varnish efficacy in preventing early childhood caries. J Dent Res 2006;85:172–176.